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Trends and risk factors analysis of NEC in preterm infants over 9 years

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Abstract

Background Investigating the trend of changes in the occurrence of necrotizing enterocolitis (NEC) in preterm infants during 9 years and analyzing the risk factors of NEC with the purpose of providing reference for clinical diagnosis and treatment of NEC.

Methods Clinical data of NEC in preterm infants with Bell's stage ≥ II from January 2013 to December 2021 in the Neonatology Department of the Third Affiliated Hospital of Zunyi Medical University was retrospectively analyzed. Trends in the occurrence of NEC in preterm infants were analyzed by the trend chi-square test. Subsequently, the general data (sex, gestational age, singleton or multiple births, birth weight, serum albumin, alkaline phosphatase, sepsis, blood transfusion, mechanical ventilation, RDS, arterial catheterization) and perinatal data (intrauterine distress, turbid amniotic fluid, premature rupture of membranes, mode of delivery, fetal heart abnormalities, diabetes mellitus) were collected; then, the risk factors for NEC were analyzed by univariate and multivariate logistic-regression analysis.

Results In the past 9 years, 77 cases of NEC occurred, with the incidence rate of 1.95%, and the incidence of NEC in preterm infants has been increasing year by year ($P < 0.05$). The results of univariate analysis showed that the morbidity of NEC in preterm infants was associated with premature rupture of membranes, blood transfusion, sepsis, and the of serum albumin ($P < 0.05$). Multivariate logistic regression analysis revealed that blood transfusion (OR = 2.232, 95% CI: 1.012–4.923) and sepsis (OR = 0.899, 95% CI: 0.809–3.915) were independent risk factors of NEC in preterm infants, while high serum albumin (OR = 0.899, 95% CI: 0.809–3.915) was an independent protective factor of NEC in preterm infants.

Conclusion The morbidity of NEC is gradually increasing. Inhibition of infection and limitation of blood transfusion are effective measures to reduce the occurrence of NEC. Meanwhile, high serum albumin is a protective factor for NEC.

Keywords Necrotizing enterocolitis, Neonates, Risk factors

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Background

Necrotizing enterocolitis (NEC) is one of the common diseases in neonates, especially in preterm infants. With the characteristics of high morbidity, high mortality rate, and high cost of treatments, survivors have been accompanied by complications, including intestinal stenosis, intestinal adhesions, cholestasis, short bowel syndrome, growth retardation, and neurodevelopmental delay, which seriously affect the quality of life of the children [1]. In recent years, as the survival rate of preterm infants increased, the incidence rate of NEC has also gradually increased. Data of 2020 showed that the global incidence of NEC in very low birth weight (VLBW) infants was about 7% [1], but the incidence of NEC was varied in various country and region due to factors such as geography, medical level, and economic level. The pathogenesis of NEC is multifactorial, so it is of great clinical significance to understand the high-risk factors for reducing the occurrence of NEC. In order to understand the latest epidemiological situation and risk factors of NEC in preterm infants in Zunyi city, the morbidity and its changing trend of NEC in preterm infants from 2013 to 2021 in the Third Affiliated Hospital of Zunyi Medical University were analyzed.

Methods

Participants

Patients included in this study abided by the inclusion criteria: (1) preterm infants diagnosed with NEC; (2) Bell's stage ≥ stage II; (3) those with complete clinical data. Despite that, there were patients who met the exclusion criteria: (1) gestational age ≥ 37 weeks; (2) Bell's stage < II; (3) combined congenital gastrointestinal anomalies, such as congenital megacolon, intestinal malrotation, intestinal atresia, gastric perforation, etc.; (4) those with incomplete clinical data. Eventually, 77 NEC preterm infants with Bell's stage ≥ II were defined as the test group, while non-NEC neonates were selected as the control group. All NEC preterm infants were diagnosed referring to Practical Neonatology, 5th Edition [2].

Data collection

General information, including name, sex, birth weight, gestational age, birth asphyxia, singleton or multiple births, feeding method, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), mechanical ventilation (sepsis, blood transfusion and serum albumin within 24 h of admission) of children with NEC, and perinatal conditions, such as premature rupture of membranes, amniotic fluid abnormalities, fetal heart abnormalities, fetal count, cesarean delivery, hypertension, diabetes mellitus, and placental inflammatory pathology, would be collected for subsequent analysis.

Statistical analysis

Enumeration data were expressed rate (%), and the χ^2 test and trend χ^2 test were used for the difference analysis. Measurement data was described as mean ± standard, and the independent sample t test was used for the comparison of the two groups. In addition, risk factors were analyzed by the univariate and multivariate logistic regression. The SPSS 25.0 software was utilized for statistical analysis, and $p < 0.05$ was considered as significant difference.

Results

General information

From January 2013 to December 2021, 3949 preterm infants were admitted to the neonatal unit (including preterm infants in the intensive care unit) of the Third Affiliated Hospital of Zunyi Medical University. Among them, 77 preterm infants with Bell's stage ≥ II NEC (1.95%) were diagnosed, and 55 males and 42 females were contained. The age of preterm infants in the test group ranged from 2 to 30 days after birth, with the mean of 16 days. The gestational age of NEC children ranged from 26^{+2} weeks to 36^{+6} weeks, and the birth weight ranged from 850 to 2950 g. During 9 years, NEC amalgamation perforated 30 people. All children with NEC were treated conservatively, and only patients with perforation needed surgical treatment. As a result, 72 cases were cured, 2 cases died, and 3 cases gave up treatments.

Incidence rate and tendency of NEC from 2013 to 2021

Information of hospitalized patients was integrated and the incidence rate of NEC tended to increase gradually by years ($P < 0.05$) (Table 1). The specific situation was as follows: in 2013, 208 premature infants were admitted, with 1 case of NEC and an incidence rate of 0.48%; in 2014, 195 premature infants were admitted, with no cases of NEC and an incidence rate of 0%; in 2015, 148 premature infants were admitted, with 3 cases of NEC and an incidence rate of 1.90%; in 2016, 197 premature infants were admitted, with 5 cases of NEC and an incidence rate

Table 1 Trends of the incidence of NEC from 2013 to 2021 (*n*, %)

Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	Trend χ^2 value	*P*-value
NEC	1 (0.48)	0 (0)	3 (1.90)	5 (2.54)	5 (0.55)	7 (1.51)	24 (4.62)	16 (2.51)	16 (2.37)	12.517	0.000

of 2.54%; in 2017, 906 premature infants were admitted, with 5 cases of NEC and an incidence rate of 0.55%; in 2018, 463 premature infants were admitted, with 7 cases of NEC and an incidence rate of 1.51%; in 2019, 519 premature infants were admitted, with 24 cases of NEC and an incidence rate of 4.62%; in 2020, 638 premature infants were admitted, with 16 cases of NEC and an incidence rate of 2.51%; and in 2021, 675 premature infants were admitted, with 16 cases of NEC and an incidence rate of 2.37%.

Trends in the incidence of NEC at different gestational age

The incidence of NEC in infants born at 28 to 31^{+6} weeks and 32 to 36^{+6} weeks increased gradually over the years ($P<0.05$). However, the incidence of NEC in infants born at less than 28 weeks did not present to be statistically significant between the years ($P>0.05$) (Table 2).

Comparison of clinical features of infants between the NEC group and non-NEC group

Significant differences were observed in albumin, blood transfusion, and sepsis between the NEC and non-NEC group ($P<0.05$). But there were no statistically significant differences in terms of gestational age, birth weight, sex, asphyxia, alkaline phosphatase, mechanical ventilation, RDA, and PDA between the two groups (Table 3). Thus, the factors, albumin, blood transfusion, and sepsis, could increase the incidence of NEC in preterm infants.

Comparative analysis of perinatal clinical factors on the two groups

The incidence of premature rupture of membranes in the NEC group was higher than that in the non-NEC group ($P<0.05$), while there was no significant difference between the two groups in terms of amniotic fluid abnormalities, fetal heart abnormalities, fetal number, cesarean section, hypertension, diabetes, and inflammatory pathological changes of the placenta (Table 4).

Multivariate logistic regression analysis for NEC

Multivariate logistics regression analysis was performed using premature rupture of membranes, albumin, sepsis, and blood transfusion, which had statistical significance in univariate logistics analysis. The results showed that sepsis (OR = 2.796, 95% CI: 1.413–5.532, $P=0.003$) and blood transfusion (OR = 2.232, 95% CI: 1.012–4.923, $P=0.047$) were independent risk factors for NEC, while high serum albumin (OR = 0. 899, 95% CI: 0.809–3.915, $P=0.047$) was an independent protective factor for the NEC (Table 5).

Discussion

Over the past three decades, the mortality rate of preterm infants has gradually decreased due to advancements in neonatal diagnosis and treatment. However, the incidence of necrotizing enterocolitis has increased, which leaded to a greater burden on patients [3]. As a result, it has become a hot spot of clinical research. For the purpose of providing clinical reference, this study analyzed the incidence of NEC in preterm infants, its changing trends, and associated risk factors over a 9-year period (from 2013 to 2021) at our hospital.

Alsaied et al. reported the global incidence of approximately 7% for necrotizing small bowel colitis in VLBW children [4]. After all, the incidence rates of NEC varied across different countries because of economic development, medical conditions, and geography. For instance, Andersone et al. reported a 9.1% incidence of NEC in preterm NICU infants in California [5], while Härkin et al. calculated a 16.58% incidence of NEC in preterm infants across Finland from 2005 to 2013 [6]. Meanwhile, Korea reported a 10-year NEC incidence of 1.19% [7], but the incidence of NEC in hospitalized newborns in Shanghai was 1.29% [8], and the incidence of NEC in very preterm infants was 4.87% in Southwest China [9]. The results of this study showed that the incidence of NEC in preterm infants in Zunyi, Guizhou province, was 1.95%, from 2013 to 2021. For preterm infants born at less than 28 weeks, the incidence rates of NEC were 7–8% in Australia, Canada, and Italy [10], while the lowest incidence of NEC for children born at 28–31 weeks was reported at 0.2% in Japan and 2–3% in other developed countries [10]. This study indicated that the incidence rate of NEC for infants born at < 28 weeks and $28–31^{+6}$ weeks in Zunyi was 5.12% and 7.43% respectively, which was higher than the reported data in Southwest China [9]. The gestational age with the highest incidence of NEC

Table 2 Trends of the incidence of NEC at different gestational age from 2013 to 2021 (*n*, %)

Gestational age (weeks)	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total	Trend χ^2 value	*P*-value
< 28	0 (0)	0(0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (4.34)	2 (5.12)	2.502	0.114
$28–31^{+6}$	0(0)	0 (0)	3 (3.57)	3 (6.98)	4 (5.88)	4 (4.88)	12 (13.33)	11 (9.4)	6 (6.74)	43 (7.43)	16.638	0.000
$32–36^{+6}$	1 (0.56)	0 (0)	0 (0)	2 (1.31)	1 (0.12)	3 (0.8)	11 (2.61)	5 (0.97)	9 (15.71)	32 (0.96)	20.043	0.000

Table 3 Comparative analysis of clinical features of infants between NEC group and non-NEC group (*n*, %)

Grouping	Gestational age [w.$\bar{x} \pm s$]	GenderMale/female [*n* (%)]	Birth weight [g.$\bar{x} \pm s$]	Choking [*n* (%)]	Alkaline phosphatase (U/L.$\bar{x} \pm s$)	Albumin (g/L,$\bar{x} \pm s$)	Blood transfusion [*n* (%)]	Mechanical ventilation [*n* (%)]	Sepsis [*n* (%)]	RDS [*n* (%)]	PDA [*n* (%)]
NEC group	31.52 ± 2.37	45/32	1623.38 ± 466.97	24 (31.17)	243.00 ± 74.30	27.32 ± 3.91	24 (31.17)	51 (66.23)	42 (54.55)	52 (67.53)	12 (15.58)
Non-NEC group	31.83 ± 2.57	49/31	1532.50 ± 420.68	22 (27.5)	241.84 ± 64.87	28.46 ± 3.91	14 (17.5)h	55 (68.75)	25 (31.25)	48 (60)	15 (18.75)
T/χ^2	−0.777	0.129	1.282	0.255	0.104	2.190	4.166	0.113	8.704	0.963	0.276
P	0.438	0.720	0.202	0.614	0.917	0.030	0.041	0.736	0.003	0.327	0.599

Table 4 Comparative analysis of perinatal clinical features between the two groups (*n*, %)

Grouping	Amniotic fluid abnormalities [*n* (%)]	Abnormal fetal heartbeat [*n* (%)]	Singleton [*n* (%)]	Cesarean delivery [*n* (%)]	Premature rupture of fetal membranes [*n* (%)]	High blood pressure [*n* (%)]	Diabetes [*n* (%)]	Inflammatory changes in the placenta [*n* (%)]
NEC	8 (10.39)	13 (16.88)	58 (75.32)	44 (57.14)	24 (31.17)	9 (11.69)	10 (12.99)	20 (25.97)
Non-NEC	7 (8.75)	12 (15)	67 (83.75)	36 (45)	18 (22.5)	8 (10)	7 (8.75)	15 (18.75)
$Z/T/\chi^2$	0.883	0.104	1.716	2.315	0.740	0.116	0.729	1.182
P	0.347	0.747	0.190	0.128	0.026*	0.734	0.393	0.277

Table 5 Multi-factor logistic regression analysis of NEC risk factors

Projects	*β*	SE	Wald	*P*	Exp (*B*)	OR (95%CI)
Albumin	−0.107	0.054	3.972	0.046	0.899	0.809 ~ 3.915
Sepsis	1.028	0.348	8.725	0.003	2.796	1.413 ~ 5.532
Blood transfusion	0.803	0.404	3.955	0.047	2.232	1.012 ~ 4.923
Constants	2.152	1.491	2.084	0.149	8.606	-

reported in this study was consistent with related studies [11, 12].

The trend analysis of incidence of NEC showed a gradual increase over time from 2013 to 2021 ($\chi^2 = 12.517$, $P = 0.000$), which was consistent with the epidemiological survey of NEC from 1987 to 2009 reported in Sweden [13] and the results of a multicenter-based epidemiological survey in China [14] suggesting a progressive increasing trend in morbidity of NEC. However, it was opposite to the results of a study in Korea which showed that the incidence of NEC is gradually decreasing from 2007 to 2017 [7] and the result of incidence of NEC, reported in Shanghai, China, which was also decreasing year by year [8], and those may have contributed to the difference of medical condition among various regions. The incidence of NEC in preterm infants in this region is increasing over times, emphasizing the need for clinical attention and the implementation of active and effective preventive measures. Early identification, early diagnosis, and early management are important to reduce its progression and to improve the immediate and long-term prognosis of the children.

NEC is a multifactorial disease, and understanding its modifiable risk factors is crucial for developing effective interventions to reduce its incidence and impact. In this regard, the results of logistics regression analysis showed that low albumin was the risk factors of NEC, which was in line with the results of previous studies [15]. Serum albumin is a negative acute phase protein that has been shown that low level of it was associated with poor clinical outcomes in critically ill children [16] and that hypoalbuminemia might serve as a marker of NEC progression [17]. Decreased level of serum albumin could lead to reduced scavenging of oxygen radicals, nitrogen radicals, and toxins, thereby impairing the antimicrobial effect increasing intestinal inflammation [18]. In addition, low serum albumin levels can result in reduced blood volume and inadequate perfusion, leading to increased intestinal ischemia and greater susceptibility to necrosis [19]. Increasing the levels of serum albumin may be one of the effective measures to reduce the incidence of NEC in preterm infants.

Moreover, this study found that sepsis was another risk factor for the development of NEC in preterm infants, which was consistent with related studies [15, 20, 21]. The incidence of NEC in children with sepsis was almost three times higher than that in children without sepsis [20]. Neonates, especially preterm infants, are susceptible to complications of infection due to their week immune system and thin skin as well as their dependence on mechanical ventilation and invasive manipulation and long-term prophylactic use of antimicrobial drugs for survival, which may increase the incidence of NEC [22]. Therefore, it is necessary for clinicians to pay attention to strategies to reduce the risk of infection exposure and take charge of antimicrobial drugs rationally.

Since McGrady et al. discovered the relationship between blood transfusion and NEC [23], the relationship between red blood cell transfusion and NEC had received extensive attention to researchers. Teiserskas et al. analyzed the relationship between red blood cell transfusion and NEC in very low birth weight infants

in a tertiary care hospital neonatal intensive care unit and found that the times and total amount of red blood cell transfusions were higher in the NEC group, when compared with the non-NEC group ($P < 0.05$) [24], and similar studies have also shown that blood transfusions increase the chance of NEC occurrence odds [25],which was in line with the results of the this study. However, some studies have shown that there is no correlation between RBC transfusion and NEC but the severity of severe anemia in VLBW infants [26, 27]. More research is needed to fully reveal the relationship between red blood cell transfusions and NEC.

Conclusion

In conclusion, the incidence of NEC in preterm infants has gradually increased in our hospital over the past 9 years, and the risk factors for NEC reported are hypoproteinemia, sepsis, and blood transfusion. This study is a single-center retrospective study which may not be generalizable to other regions. And a larger sample sizes, prospective designs, and more comprehensive analysis studies are expected.

Abbreviations

NEC	Necrotizing enterocolitis
VLBW	Very low birth weight
RDS	Respiratory distress syndrome
PDA	Patent ductus arteriosus

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Not applicable.

Author's contributions

Y L designed the project. Y Y and Q H collected the clinical information and finished the manuscript. M Y and PL Z performed the data analysis. LJ S helped with information collection. All author approved the manuscript and agreed to publish it.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This research was reviewed and approved by the institutional review board of the Third Affiliated Hospital of Zunyi Medical University, with the protocol number ethical review (2022)-311. Written informed consent was obtained from all parents and/or legal guardian of enrolled children. All the methods were carried out in accordance with ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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